Challenges of interpreting CMV DNAemia and its potential association with chronic lung disease in children and adolescents with perinatally acquired HIV infection

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Dear Editor,

It is with great interest that we read the article by Yindom *et al.* who performed an observational study reporting a high prevalence of CMV DNAemia among older children and adolescents with perinatally acquired human immunodeficiency virus (PHIV), and an independent association of DNAemia >1000 copies/mL with stunting and reduced lung function[1]. We wish to highlight some caveats that in our opinion are pertinent when interpreting the reported findings.

The authors investigated the hypothesis that poorly controlled CMV co-infection acquired in childhood could contribute to comorbidities such as chronic lung disease (CLD), but the evidence presented does not adequately test this hypothesis. First, adjustment for potential confounders was limited. In the same population, late initiation of antiretroviral treatment and poor nutrition were also associated with decreased lung function [2]. CLD described in people living with HIV (PLWH) is also associated with a history of frequent respiratory tract infections with clinical and radiological findings suggestive of repeated bacterial infections[3]. The interplay between CMV and HIV is complex, and it is questionable whether subclinical CMV replication in the bloodstream is a causal agent leading to complications or merely a marker of impaired cellular immunity[4, 5]. The observed association could, therefore, be confounded by associated defects in cell-mediated or innate immunity, precluding sufficient control of both CMV and bacterial infections. For example, alveolar macrophage (AM) microbicidal responses are impaired in PLWH, despite adequate antiretroviral therapy and independent of CD4 count, predisposing to bacterial pneumonia [6]. However, AM from CMV seropositive individuals are permissive to CMV re-activation and lytic replication, and potentially associated interference with immunological function[7, 8]. Therefore, CMV replication in the lung in the absence of overt pneumonitis could indeed predispose to repeated episodes of bacterial infection, but the data reported in this study cannot confirm this as the

direct evidence of CMV replication in the lungs was not studied. Whilst we recognize the extreme difficulties in obtaining lower respiratory tract specimens in this setting, this does pose a barrier to attributing causality to CMV.

Additionally, the authors reported CMV DNAemia as copies/mL. The World Health Organization International Standard for CMV recommends calibrating results to international units per ml (IU/ml) to prevent large inter-laboratory heterogeneity. This variability is not only problematic for laboratories, but also clinicians and patients, and can be as large as 6 $\log_{10}$[9, 10]. Therefore, reported DNAemia values are difficult to interpret, and viral loads cannot be translated into other settings.

Considering these points, CLD is likely to have a multifactorial aetiology in this population, and although an interesting hypothesis, an independent association between CMV DNAemia and CLD remains unconfirmed in this population. We agree that further work is required to refine our understanding of CMV DNAaemia and CLD. This will require sampling the lower respiratory tract, calibrating quantitative CMV viral load results to the international standards and including other relevant potential confounders in time-varying multivariable analysis, which are necessary to determine if trials of antivirals against CMV in this particular setting are warranted.

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Conflict of Interest:

The authors declare that there is no conflict of interest

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